REMARKS

Claims 80-90 are now pending in the application. Applicants would like to thank the Examiner for the courtesies extended to Applicants' representative during the telephonic interview of June 14, 2007. The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks contained herein.

REJECTION UNDER 35 U.S.C. § 112

Claims 88 and 90 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed. However, Applicants have elected to amend Claims 88 and 90 to recite "consisting of" rather than "consisting essentially of", which is believed to obviate the present rejection. According to the Examiner, such amendment will be sufficient to overcome the stated rejection. Reconsideration and withdrawal of the present rejection are respectfully requested.

Claims 88 and 90 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirements. This rejection is respectfully traversed. However, Applicants have elected to amend Claims 88 and 90 to recite "consisting of" rather than "consisting essentially of", which is believed to obviate the present rejection. According to the Examiner, such amendment will be sufficient to overcome the stated rejection. Reconsideration and withdrawal of the present rejection are respectfully requested.

Claims 80-90 stand rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification, as failing to comply with the enablement requirement. This rejection is respectfully traversed.

During the telephonic interview, the Examiner stated that it was her position that the specification does not teach how to use the "formula" for classifying and predicting the survival rate of DLBCL patients, which allows one of ordinary skill in the art to practice the claimed invention and that one would be forced into undue experimentation. In fact, the Examiner alleged that the Applicants did not provide any evidence in the specification that they in fact used the "formula". However, as discussed during the telephonic interview, Applicants submit that the originally-filed application does enable one of ordinary skill in the art to practice the invention and, further, that the Applicants provided evidence of how to use the present invention.

I. *The Originally Filed Specification Is an Enabling Disclosure*

Applicants respectfully submit that the specification, as originally filed, provides ample specificity to enable one skilled in the art to practice the invention without undue experimentation. As the Examiner correctly stated, the factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In connection with the present application, Applicants respectfully submit that (1) practicing the present invention in accordance with the specification will require little to no experimentation, (2) the originally filed specification provides more than enough direction and guidance, (3) the originally filed specification includes working examples, (4) the nature of the invention is well within the understanding of those having ordinary skill in the art, (5) the state of the prior art provides sufficient background, (6) those skilled in the art are learned professionals

well versed in such technology, and (7) the claims are sufficiently tailored to focus on these novel features.

To address many of these factors, Applicants submit herewith a copy of an Information Disclosure Statement filed May 5, 2005, and initialed by the Examiner. In this Information Disclosure Statement, Applicants cited an article published in the New England Journal of Medicine authored by the inventors of the present application entitled "Prediction of Survival in Diffuse Large-B-Cell Lymphoma Based on the Expression of Six Genes" (hereinafter "Applicants' NEJM Article"). As should be appreciated, the New England Journal of Medicine is a highly-regarded, weekly general medical journal that publishes new medical research findings, review articles, and editorial opinion on a wide variety of topics of importance to biomedical science and clinical practice. Applicants' NEJM Article mirrors the teachings of the present application and provides equal breadth of information regarding the invention, its use, and the particulars surrounding its discovery and practicality as the originally-filed specification. Applicants' NEJM Article outlines the identical formula model set forth in Paragraph [0043] of the present application and the identical figures and description of the results as illustrated in the present application. In sum, Applicants' NEJM Article is nearly identical in its teachings and enablement to the present application.

With this in mind, Applicants submit that the publication of the teachings, formula model, figures, and other disclosure of the present application, as an article in the New England Journal of Medicine, is indicative that (1) the present application sufficiently enables those skilled in the art to practice the present invention without undue experimentation, (2) the originally filed specification provides more than enough direction and guidance, (3) the nature of the invention is well within the expertise of those having ordinary skill in the art, and (4) those skilled in the art will readily appreciate the industry leading advancements that the present invention provides.

Moreover, Applicants submit that it would be counter-intuitive to argue that the present specification does not adequately enable one skilled in the art to practice the invention without

undue experimentation in light of the fact that the similar disclosure has been reviewed, accepted, and published in an industry leading peer-review publication, namely the New England Journal of Medicine.

II. *The Originally Filed Specification Provides Numerous Instances Where Applicant Use the Formula Model to Predict Survivability*

Applicants submit that the originally-filed specification provides sufficient proof that Applicants had possession of the present invention and used the present invention to prove success of the present invention.

In discussions with the Examiner, it appears there is confusion surrounding various examples set forth in the specification and whether Applicants used the claimed formula model (see Paragraph [0043] of the specification) as part of these examples. Applicants submit that it should be readily apparent from the specification that such formula model was used as part of the examples to validate the formula model. To establish this fact, Applicants submit the following excerpts from the originally-filed specification (emphasis added; "*[Eq. 1]*" added to illustrate that the discussed "model" represents the formula set forth in Paragraph [0043]):

> [0042] **Since this analysis established an inter-correlation between the expressions of these 6 genes and survival, we constructed a model based on a weighted predictor derived from the relative contributions of each gene in the multivariate analysis. The weighted predictor (z) was calculated for each tumor specimen and the tumors were ranked into 3 tertiles: low, medium and high** using the -0.63 and 0.093 as cut points (<-0.063--low risk, between -0.063 to <0.093, medium risk and >0.093--high risk groups). The overall survival of these 3 groups was significantly different (p=0.004) with 5-year survival of 65%, 49% and 15% for the low, medium and high groups, respectively (mean overall survival [95% confidence interval] of 7.1 {5.4--not achieved}, 9.0 { 1.1--not achieved} and 4.5 {1.2-4.3} years, respectively, FIG. 2). Consequently, patients with tumors expressing high levels of LMO2, BCL-6 and FN1 and low levels of CCND2, SCYA3 and BCL-2, survived longer.

[0043] **For construction of the survival prediction model, we derived the weighted predictor (Z) from the multivariate analysis for each of the six genes:**

$$Z=(-0.0273xLMO2)+(-0.2103xBCL6)+(-0.1878xFN1)+(0.0346xCCND2)+(0.1888xSCYA3)+(0.5527xBCL2). \quad [Eq. 1]$$

[0044] Thus for example the negative weight on LMO2 means that higher expression correlates with lower risk (longer survival). The positive weight on CCND2 means that higher expression correlates with higher risk (shorter survival).

EXAMPLE 3

[0045] **This example illustrates the validation of the survival prediction model** *[Eq. 1].*

[0046] **To validate the usefulness of the model derived in Example 2, the model** *[Eq. 1]* **was applied to two independent previously published DLBCL gene expression data sets derived from DNA microarray methodology** (Shipp et al., supra, 2003; Rosenwald et al., supra, 2003). **Application of the 6 gene prediction model** *[Eq. 1]* **to data from Shipp et al.** (Shipp et al., supra, 2003)**(FIG. 3A) and to that of Rosenwald et al.** (Rosenwald et al., supra, 2002) **(FIG. 3b) confirmed its ability to predict survival since it could stratify DLBCL cases into 3 subgroups with statistically significant different overall survival** (P=0.03 and P=0.0004, respectively). Although in the smaller DLBCL cohort reported by Shipp et al., the overall survival of the group in the medium tertile was similar at the 5 year point to that of their high risk tertile, this medium tertile did have an intermediate risk in the larger cohort of patients analyzed by Rosenwald et al. (Rosenwald et al., supra, 2002) (FIG. 3B).

[0047] **We next analyzed whether this prediction model** *[Eq. 1]* **could add to the prognostic value of the IPI.** In our own series of 66 patients there were not enough patients in the lowest risk IPI group to achieve statistical significance. But in our patients within the high clinical risk IPI group, the six gene expression model could further subdivide the patients in respect to survival (P=0.006) (data not shown). **We, therefore, tested the model** *[Eq. 1]* **on the larger DLBCL data set** derived from microarray analysis reported by Rosenwald et al. (Rosenwald et al., supra, 2002) (FIG. 4). We used their same three subdivisions of the patients according to the IPI (low, medium and high risk). **Within each of these subgroups we further divided the patients according to the 6 gene expression model** *[Eq. 1].* In some of these groups the patients numbers were limited. **But in each IPI strata we could identify an especially poor surviving group (FIG. 4 blue lines). By combining the lowest surviving tertiles**

from the medium and high risk IPI strata, then we identify 30% of all patients that receive very little benefit from current therapy.

[0048] **The present study defined and validated across the published studies a small set of genes whose expression can predict DLBCL survival and which can be measured by a clinically applicable method** *[Eq. 1]*. To this end, we evaluated side-by side the prognostic significance of 36 representative genes chosen based on the previous reports suggesting their prognostic potential or from our own analysis of the existing microarray data (Table 1). **We have designed a prediction model of overall survival consisting of 6 genes** *[Eq. 1]* **that subdivided DLBCL patients into three prognostic groups** in our series of 66 patients and in independent groups of 58 and 240 DLBCL tumors analyzed by Shipp et al. (Shipp et al., supra, 2002) and Rosenwald et al. (Rosenwald et al., supra, 2002), respectively. The validation of our model did not require any adjustments of the published microarray data or any refinements of our gene list. Moreover, this model could further sub-classify DLBCL patients within IPI strata into longer- and shorter-term survivors. The genes comprising this model are present in each of the previously denoted lymphocyte signatures such as germinal (LMO2 and BCL-6), activated B cell (BCL-2, CCND2, SCYA3) and lymph node signatures (FN1) (Alizadeh et al., supra, 2000; Rosenwald et al., supra, 2002). However, the model is independent of these signatures and several genes associated with these signatures do not carry predictive power in our model.

Applicants submit that it is clear that, at the time of the application, Applicants possessed and provided sufficient specificity and proof of the success of the present invention, in particular the prediction model set forth as the equation of Paragraph [0043]. If the Examiner believes that the specification would benefit from the addition of the "*[Eq. 1]*" terms as used herein, Applicants is willing to add such notations to the specification. Otherwise, the present Amendment should provide sufficient record.

Reconsideration and withdrawal of the present rejection are respectfully requested.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner

reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

Dated: June 15, 2007

By: _____
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Sheet 1 of 1

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Levy et al.	
FILING DATE	GROUP
March 3, 2004	1642

U.S. PATENT DOCUMENTS

Ref. Desig.	Examiner's Initials	Document Number	Date	Name	Class/ Subclass	(If appropriate) Filing Date
1.						

FOREIGN PATENT DOCUMENTS

Ref. Desig.	Examiner's Initials	Document Number	Date	Country	Class/ Subclass	Translation Yes	No
1.							

OTHER DOCUMENTS (including Author, Title, Date, Pertinent Pages, etc.)

Ref. Desig.	Examiner's Initials	
1.	LY	Hans, C.P. et al.; "Confirmation of the molecular classification of diffuse large B-cell lymphoma by imunohistochemistry using a tissue microarray"; Blood; Vol. 103, No.1; September 22, 2003; pgs. 275-282.
2.	LY	Lossos, I.S. et al.; "Prediction of survival in diffuse large B-cell lymphoma based on the expression of six genes"; The New England Journal of Medicine; Vol. 350, No. 18; April 29, 2004; pgs. 1828-1837.
3.	LY	Wright, G. et al.; "A gene expression based method to diagnose clinically distinct subgroups of diffuse large B cell lymphoma"; Proceedings of the National Academy of Sciences of the United States of America"; Vol. 100, No. 17, August 19, 2003

Examiner:	LY /Lei Yao/	Date Considered:	09/13/2006

EXAMINER: Please initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.